ORGANIC LETTERS

2000
Vol. 2, No. 17
2575−2578

Total Synthesis of Epothilone A

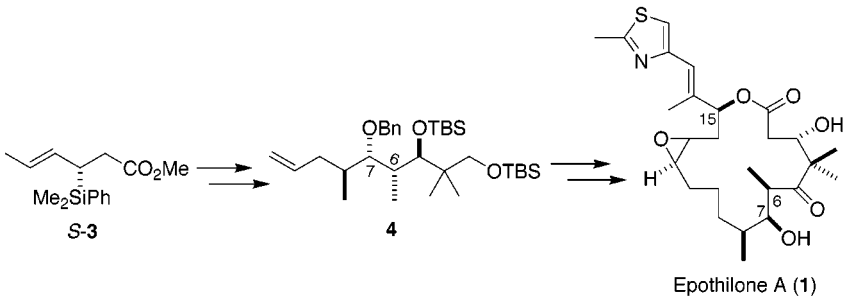
Bin Zhu and James S. Panek*

Department of Chemistry and the Center for Streamlined Synthesis, Metcalf Center for Science and Engineering, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215

panek@chem.bu.edu

Received May 25, 2000

ABSTRACT



Epothilones A (1) and B (2) are potent antitumor natural products with a Taxol-like mechanism of action. A total synthesis of epothilone A (1) is reported, which utilized chiral silane-based bond construction methodology to introduce the key C-6 and C-7 stereocenters of fragment 4. The C-15 stereocenter of fragment 5 was established by a lipase-mediated kinetic resolution. The fragments were assembled with a Suzuki coupling reaction and an aldol condensation and cyclized with a Yamaguchi-type macrolactonization reaction.

Epothilones A (**1**) and B (**2**) are cytotoxic macrolides isolated from the myxobacterium *Sorangium cellulosum*.[1] These compounds exhibit potent antitumor activity, and their mechanism of action is found to be similar to that of Taxol (paclitaxel).[2] Both epothilones and taxanes kill tumor cells through induction of tubulin polymerization and microtubule stabilization. Moreover, it has been recognized that epothilones are effective against a number of Taxol-resistant tumor cell lines. As a consequence of their remarkable biological activity and unique chemical structure, extensive effort concerning the synthesis of the epothilone class of molecules was initiated and is manifested in the large number of publications in this area.[3] However, the development of novel and convergent synthetic routes toward these compounds would constitute a useful contribution to this field.

We report herein a highly convergent synthesis of epothilone A (**1**), which is based on the synthesis and transition metal catalyzed cross coupling of two advanced intermediates: polypropionate-derived fragment **4** and thiazole-containing fragment **5**. Chiral silane-based bond construction methodology[4] was utilized for the introduction of the C-6 and C-7 stereocenters of the polypropionate-derived fragment **4**. The chiral silane reagents (Figure 1) developed in our laboratory

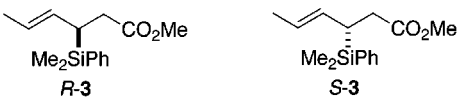


Figure 1. Chiral crotylsilane reagents.

have demonstrated their usefulness in a number of complicated natural product syntheses.[5] The chirality of these silicon-bearing reagents is derived from a *Pseudomonas* AK lipase[6] mediated kinetic resolution.[7] This biocatalytic process

(1) (a) Gerth, K.; Bedorf, N.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1996**, *49*, 560−563. (b) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem., Int. Ed, Engl.* **1996**, *35*, 1567−1569.

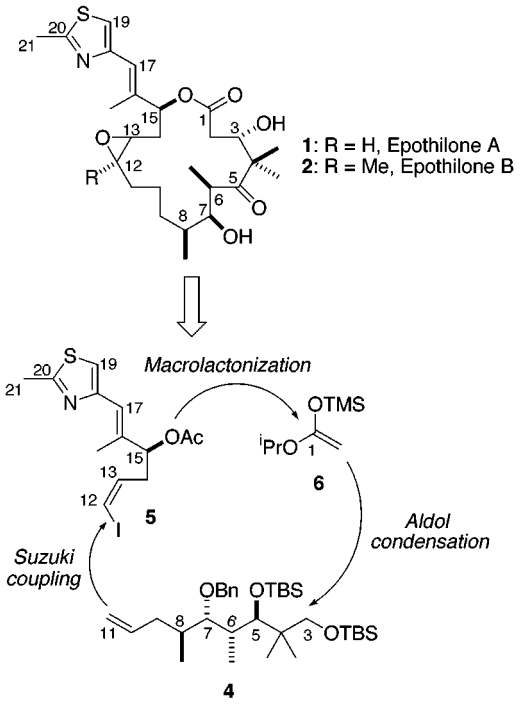
(2) Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325−2333.

10.1021/ol006104w CCC: $19.00
Published on Web 07/26/2000

is the ultimate source of enantioenriched materials used in our synthesis of epothilone A (**1**).

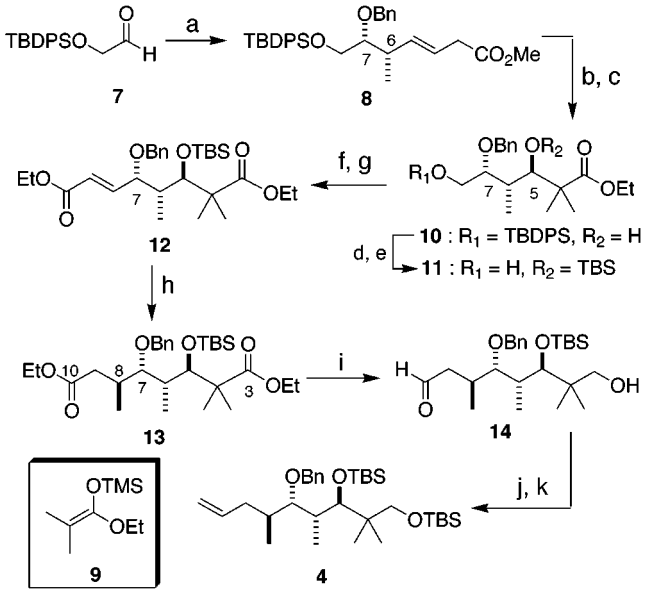
Scheme 1 outlines the retrosynthetic analysis of epothilone A (**1**). The illustrated bond disconnection gave three fragments, **4**, **5**, and **6**. The 16-membered lactone was to be assembled using an intermolecular Suzuki cross coupling of **4** and **5** and a diastereoselective aldol condensation with silyl ketene acetal **6** followed by a Yamaguchi-type macrolactonization.

Scheme 1. Retrosynthetic Analysis of Epothilone A (**1**)



The synthesis of fragment **4** is shown in Scheme 2. Aldehyde **7** was first converted into the di-benzyl acetal (TMSOBn, catalytic TMSOTf), which was then treated with chiral crotylsilane reagent *S*-**3** in the presence of $BF_3{\cdot}Et_2O$ to give the desired crotylation adduct **8** in 83% yield and good diastereoselectivity (*syn*/*anti* = 15:1).[8] The double bond of **8** was oxidatively cleaved, and the resulting aldehyde was subjected to a chelation-controlled aldol condensation with silyl ketene acetal **9** under the catalysis of $TiCl_4$.[9] The aldol product **10** was obtained in 83% yield and in a 6:1 ratio favoring the desired C5−C7 *anti* diastereomer. The secondary hydroxyl group of **10** was protected as a *tert*-butyldimethylsilyl (TBS) ether, and the existing primary *tert*-butyldiphenylsilyl (TBDPS) protecting group was selectively removed using acetic acid buffered tetrabutylammonium fluoride to give the alcohol **11**. A Swern oxidation and a Wittig olefination reaction converted **11** into the α,β-unsaturated ester **12**, which was then treated with Me_2CuLi in the presence of trimethylchlorosilane (TMSCl) at low temperature (−78 °C, THF). The cuprate addition reaction proceeded smoothly to give the 1,4-adduct **13** in 94% yield with a C8−C7 *anti*/*syn* ratio greater than 10:1.[10] Gratifyingly, the two ester groups of **13** were easily differentiated by a DIBAL-H reduction using CH_2Cl_2 as solvent, which cleanly transformed the C-10 and C-3 esters to an aldehyde and a primary hydroxyl group, respectively.[11] The resulting hy-

Scheme 2. Synthesis of Fragment **4**[a]



[a] (a) TMSOBn, catalytic TMSOTf, CH_2Cl_2, −78 to −50 °C, 16 h; *S*-**3**, $BF_3{\cdot}Et_2O$, −30 °C, 24 h, 83%, *syn*/*anti* = 15:1; (b) O_3, MeOH/CH_2Cl_2 (2:1), pyridine, Me_2S, −78 °C to rt, 88%; (c) $TiCl_4$, **9**, CH_2Cl_2, −78 °C, 30 min, 83%, *anti*/*syn* = 6:1; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h, 95%; (e) Bu_4NF/AcOH (1:1), THF, rt, 24 h, 92%; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 95%; (g) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 4 h, 91%; (h) Me_2CuLi, TMSCl, THF, −78 °C, 4 h, 94%, *anti*/*syn* > 10:1; (i) DIBAL-H, CH_2Cl_2, −78 °C, 15 min; (j) TBSCl, imidazole, DMF, 68% for two steps; (k) CH_3PPh_3Br, $NaN(TMS)_2$, THF, 0 °C, 90%.

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(4) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1316.

(5) (a) Panek, J. S.; Xu, F. *J. Am. Chem. Soc.* **1995**, *117*, 10587−10588. (b) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1998**, *63*, 4572−4573. (c) Hu, T.; Panek, J. S. *J. Org. Chem.* **1999**, *64*, 3000−3001. (d) Hu, T.; Panek, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 9229−9230. (e) Liu, P.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 1235−1236.

(6) *Pseudomonas* AK lipase was purchased from Amano International Enzyme Co. for $100/100 g.

(7) Beresis, R. T.; Solomon, J. S.; Yang, M. G.; Jain, N. F.; Panek, J. S. *Org. Synth.* **1997**, *75*, 78−88.

(8) Panek, J. S.; Yang, M. *J. Org. Chem.* **1991**, *56*, 5755−5792.

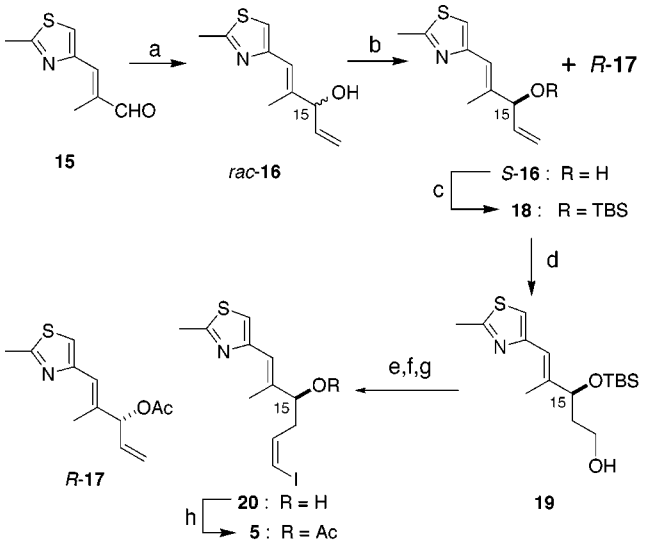
(9) For chelation-controlled addition to carbonyl see: Reetz, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556−569.

(10) (a) Hanessian, S.; Sumi, K. *Synthesis* **1991**, 1083−1089. (b) Hanessian, S.; Wang, W.; Gai, Y.; Oliveier, E. *J. Am. Chem. Soc.* **1997**, *119*, 10034−10041.

droxy aldehyde **14** was protected as a silyl ether, and the aldehyde moiety was subjected to a Wittig olefination reaction to install the terminal olefin and furnish the C3−C11 fragment **4**.

The synthesis of C12−C21 fragment **5** started with the known aldehyde **15**.[12] Treatment of **15** with vinylmagnesium bromide (−78 °C, THF) led to racemic divinyl carbinol *rac*-**16**. An enzymatic kinetic resolution of *rac*-**16** using *Pseudomonas* AK lipase provided enantiomerically enriched alcohol *S*-**16** in 48% yield (50% conversion) and 90% ee ($E = 58.4$),[13] along with the enantiomeric acetate *R*-**17**.[3g] This alcohol *S*-**16** was then protected as its silyl ether to give **18** (TBSCl, imidazole, DMF). Selective hydroboration of the terminal olefin of **18** with dicyclohexylborane followed by oxidation led to alcohol **19**. This intermediate was converted into the *cis*-vinyl iodide **20** by a three-step sequence, including Dess−Martin oxidation,[14] Wittig olefination, and HF-promoted desilylation. Acetylation of **20** finished the synthesis of the C12−C21 fragment **5** (Scheme 3).

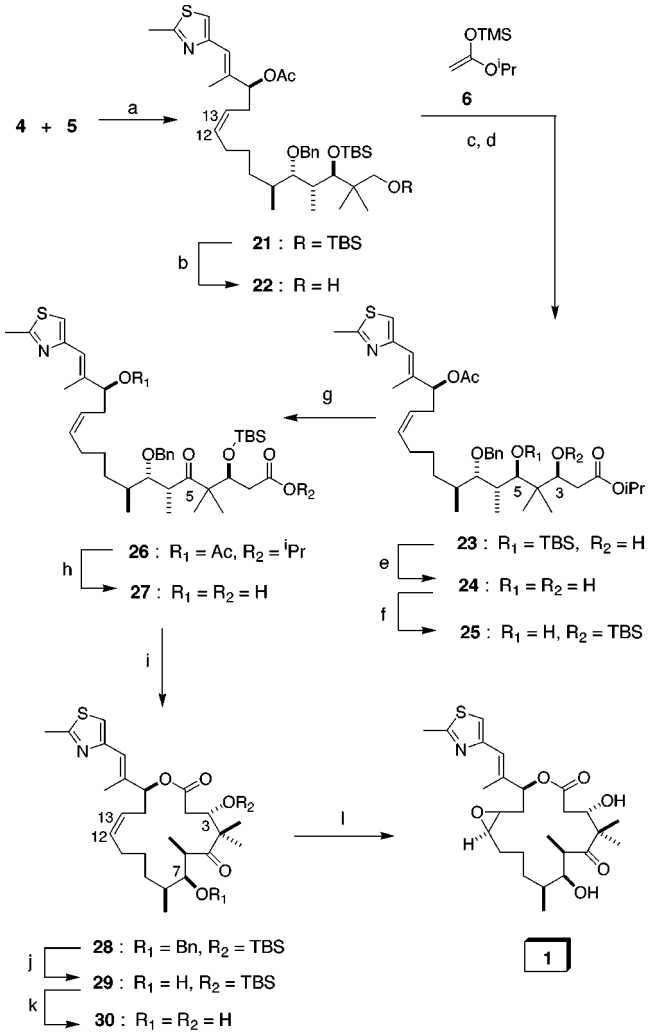
Scheme 3. Lipase Resolution and Synthesis of Fragment **5**[a]



[a] (a) Vinylmagnesium bromide, THF, −78 °C, 90%; (b) lipase AK (50wt %), vinyl acetate, hexane, rt, 48 to 72 h, 48%, 90% ee; (c) TBSCl, imidazole, DMF, 95%; (d) BH_3·THF, cyclohexene, THF, NaOH, H_2O_2, 90%; (e) Dess−Martin periodinane, CH_2Cl_2; (f) CH_2IPPh_3I, $NaN(TMS)_2$, THF; (g) HF (48% aqueous), CH_3CN, 65% for three steps; (h) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 95%.

In a manner similar to Danishefsky's synthesis, an intermolecular Suzuki coupling of fragments **4** and **5** was successfully carried out to give the coupling product **21** with the desired C12−C13 *cis*-olefin as a single double bond isomer (Scheme 4).[15] Compound **21** was selectively deprotected at the primary position to give alcohol **22**. Dess−Martin oxidation of the primary hydroxyl group of **22** provided the corresponding aldehyde, which was then treated

Scheme 4. Synthesis of Epothilone A (**1**)[a]



[a] (a) **4**, 9-BBN, THF; then **5**, $Pd(dppf)Cl_2$, Cs_2CO_3, DMF, H_2O, rt, 60%; (b) HF/pyridine, THF, rt, 93%; (c) Dess−Martin periodinane, CH_2Cl_2, 91%; (d) **6**, $TiCl_4$, CH_2Cl_2, −78 °C, 15 min, 87%, *syn*/*anti* = 9:1; (e) Bu_4NF, THF, 0 °C, 10 min, 89%; (f) TBSCl, imidazole, DMF, rt, 36 h, 91%; (g) Dess−Martin periodinane, CH_2Cl_2, 93%; (h) NaOH (aq), MeOH, reflux, 1.5 h, 62%; (i) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 0 °C, 15 min; DMAP, toluene, rt, 30 min, 73%; (j) DDQ, CH_2Cl_2/H_2O (4:1), rt, 82%; (k) 20% CF_3CO_2H in CH_2Cl_2, rt, 2.5 h, 90%; (l) CH_3CN, H_2O_2 (30% aqueous solution), $KHCO_3$, MeOH, rt, 24 h, ca. 60% (based on recovered starting material).

(11) A possible explanation for different behavior of C3 and C10 ester groups in DIBAL-H reduction is due to their different steric enviroment.

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with the silyl ketene acetal **6** in the presence of $TiCl_4$. The aldol condensation produced the desired β-hydroxy ester **23**, along with its C3 epimer in a 9:1 ratio and in 87% combined yield. Desilylation at the C5 position followed by selective protection of the C3 hydroxyl group afforded compound **25**. At this point, the C5 hydroxyl was oxidized to ketone **26**. Base-promoted hydrolysis of C-1 isopropyl ester and C-15 acetate of **26** furnished the hydroxy acid **27**, which was subjected to a Yamaguchi-type macrolactonization reaction to give lactone **28**.[16] The protecting groups of the C7 and C3 hydroxyls were subsequently removed by treatment of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and trifluoroacetic acid to produce the di-hydroxy lactone **30**. Finally, epoxidation of the C12−C13 *cis*-olefin with in situ generated methyl peroxycarboximidic acid led to epothilone A (**1**).[17]

In summary, we have successfully carried out a highly convergent synthesis of epothilone A. Chiral silane-based bond construction methodology was employed to install the key C6 and C7 stereocenters. A kinetic resolution with *Pseudomonas* AK lipase was used to provide the enantiomerically enriched thiazole subunit. Noteworthy, the materials for the synthesis are not obtained from the "chiral pool", and the enantioenriched materials are derived from one chiral source—*Pseudomonas* AK lipase.

Acknowledgment. Financial support was obtained from the NIH (GM 55740). We thank Professor Samuel J. Danishefsky (The Sloan-Kettering Institute for Cancer Research) for copies of NMR spectra of epothilone A and several intermediates.

Supporting Information Available: Experimental details and characterization of compounds **1**, **4**, **5**, **7**, **8**, **10**−**13**, and **16**−**30**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006104W

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